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Im Auftrag

For the President of the European Patent Office

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
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Biodegradable, biocompatible implant

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Biodegradable, biocompatible implant

The present invention concerns an biodegradable, biocompatible implant for the treatment of defects in a living organism such as bone defects or tooth extraction wounds.

INTRODUCTION AND BACKGROUND OF THE INVENTION

Bone defects can be treated by the implantation of an autograft, an allograft, or a xenograft in the healing site. However, these biological implants suffer of many drawbacks, among them, for example, shortage of donor tissue, bacterial and viral contamination, etc. Biocompatible synthetic implants may present a safe and effective alternative for many indications.

In dental treatment, for example, the extraction of a tooth leaves an open wound that might be contaminated by bacteria. Moreover, it is a known problem, that due to the absence of the tooth, alveolar bone spontaneously undergoes remodeling, leading to its atrophy. Such atrophy may then cause many complications for subsequent reconstruction. In order to prevent this process, it has been suggested to implant into the extraction site a biocompatible, biodegradable open porous implant, which is configured and dimensioned to fit inside the tooth extraction socket. Unfortunately, the process of bone tissue regeneration competes with faster-growing soft tissue and epithelial cells, which tend to fill the bone repair site before sufficient bone growth is induced even when a osteoconductive scaffold is present.

To overcome this problem it is known from the prior art to employ a barrier material which is applied over the implant to exclude competitive cells and to avoid the migration of microscopic materials. This process is known as guided bone regeneration and involves a surgical placement and insertion of a barrier membrane which prohibits the in-growth of soft tissue and epithelial cells. Usually, after the initial surgical procedure, a removal of

the membrane is necessary in order to avoid later inflammation and infection. There are also known biodegradable membranes which obviate the need for a subsequent removal operation. Nevertheless, these membranes are difficult to handle and implant. The surgical process is time consuming, cumbersome to the patient and involves considerably high costs.

In order avoid the drawbacks of the known prior art treatments with surgically placed membranes in WO 00/35510 it is suggested to provide the osteogenic bone graft with a zone of impermeability to soft tissue. The osteogenic bone graft comprises a coherent mass of bone particles from porcine of bovine bone. The zone of impermeability is obtained by reducing the porosity of a portion of the surface of the bone osteogenic graft. This is achieved, e.g., by heating a portion of the surface area of the coherent bone mass, by crosslinking a portion of the surface area of the coherent bone mass and/or by applying one or more biocompatible masses to a portion of the surface area of the coherent bone mass to provide a microporous layer thereon and by combinations of the processes. By this treatment the zone of impermeability is formed as an integral, indivisibly interconnected portion of the osteogenic bone graft so as to form a single, unified whole which distinguishes from bone grafts which are combined with a separate barrier membrane material.

While the osteogenic bone grafts of WO 00/35510 avoid the drawbacks of prior art bone grafts which may be or may not be combined with surgically placed barrier membranes they too suffer from drawbacks. The base material for the bone particles usually is a natural, organically obtained porcine or bovine bone with all naturally occurring inadequaties. The obtaining of the bone particles from bones of organisms necessitates careful purification steps in order to avoid organic and genetic impurities. The production process may also require demineralization procedures to ensure that the inorganic mineral content is reduced to the required extent to obtain the desired porosity. These procedures are time consuming, cumbersome and involve considerable apparative and laborious efforts. The resultant product, thus, is rather scarce and costly. Moreover, the bone grafts from bone particles degrade very slowly and are rather incorporated in the host bone tissue.

While the problems of the prior art have been described with reference to dental problems it will be appreciated by those skilled in the art that implants are also used as treatments for other skeleton parts. If, for example, a part of the skeleton is stricken by a tumor, the area stricken by the tumor may be removed and replaced by an implant. In that case with the implants known from the prior art similar problems as those described with respect to dental treatments may arise.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of the present invention to overcome the drawbacks of the prior art bone grafts and osteoconductive scaffolds. There is to be provided a biocompatible and biodegradable implant for the treatment of defects in a living organism such as bone defects or extraction wounds which reliably prohibits an in-growth of faster growing soft tissue and epithelial cells into the implantation site. A surgical placement and later removal of barrier membranes shall be avoided. There is to be provided a biocompatible and biodegradable implant having a controllable open interconnected macro porosity, which allows an in-growth of regenerating bone tissue. It is a further object of the present invention to provide a biodegradable biocompatible implant which may be assembled and shaped easily in the desired manner to a defect-analogous implant in order to avoid hollow spaces between the implant and the sidewalls of the cavity. The biodegradable biocompatible implant shall be made of reproductively obtainable base materials. The base materials shall be of synthetic nature and shall allow an easy preparation of the biocompatible and biodegradable implant.

The biodegradable, biocompatible implant according to the invention are only made of synthetic, biocompatible and biodegradable materials. In the present invention, the synthetic biocompatible and biodegradable materials are defined as any biocompatible and biodegradable materials, which are not derived from tissues of vertebrate animals.

In the present invention, the following biocompatible and biodegradable materials are considered as synthetic materials:

- chitin and chitosan, which may be derived from tissues of marine non vertebrate animals,
- hyaluronic acid, a polysaccharide, which can be obtained from rooster comb or by micro-organism fermentation.
- poly(amino acids) and polypeptides, which may be produced by biotechnological processes.
- any polysaccharide, which is obtained from plants , from non vertebrate animals or by biotechnological processes. As example for such polysaccharide, we can mention alginate.

According to the invention an implantable biodegradable, biocompatible implant for the filling of a cavity in a living organism such as, for example, a bone defect or an extraction wound, is suggested comprising an open porous scaffold which is made for example from synthetic, biocompatible and biodegradable granules, and further comprising a biodegradable biocompatible membrane which is sealed to a surface portion of the scaffold such, that the scaffold and the membrane form a single piece of matter.

The scaffold can be obtained by fusing together granular biomaterial. Granules from synthetic, biocompatible and biodegradable materials are known in the art. They are obtainable in relatively simple processes and may be formed in reproducible shapes, porosities and sizes in any desired quantity. Time consuming, costly purification and demineralization processes are not necessary. The zone of impermeability is formed by a biodegradable membrane. Such membranes are known from the prior art, e.g., as surgically applied barrier membranes. They have the required barrier function and biocompatibility. The membrane is sealed to the exposed surface of the scaffold. Thus, the interconnected scaffold and membrane form a single piece of matter which may be handled like a scaffold without membrane. The shape of the membrane is ideally matched to the shape of the exposed surface of the scaffold. Thus, there is no need for an alignment of the membrane after the insertion of the scaffold.

A surgical placement and later removal of the barrier membrane is not required. The biodegradable biocompatible implant according to the invention consists of the scaffold and of the barrier membrane. The two components are distinct from each other, but they are practically inseparably connected with each other. The biodegradable biocompatible implant may be simply inserted into a bone defect or an extraction wound. The membrane on top of the exposed surface of the scaffold provides a safe barrier against an in-growth of faster growing soft tissue and epithelial cells into the implantation site. The process steps for the production of the biodegradable biocompatible implant are relatively simple and may be accomplished by the skilled physician or his assistance on location. Furthermore, standard forms of the biodegradable biocompatible implant may be produced as cones, cubes, cylinders, etc. at the manufacturing site, which can then be adapted by the physician as necessary. These standard biodegradable biocompatible implants may contain a membrane covering at least one zone of the surface of the biodegradable and biocompatible implant. The manufacture process is easy and fast to accomplish, resulting in comparatively low costs, which is an additional benefit for the patient.

The synthetic biocompatible, biodegradable scaffold may be formed by fusing together granules made of a synthetic, biocompatible and biodegradable material, such as biopolymers, bioglasses, bioceramics, more preferably calcium sulfate, calcium phosphate such as, for example, monocalcium phosphate monohydrate, monocalcium phosphate anhydrous, dicalcium phosphate dihydrate, dicalcium phosphate anhydrous, tetracalcium phosphate, calcium orthophosphate phosphate, calcium pyrophosphate, α-tricalcium phosphate, β-tricalcium phosphate, apatite such as hydroxyapatite, or polymers such as, for example, poly(α-hydroxyesters), poly(ortho esters), poly(ether esters), polyanhydrides, poly(phosphazenes), poly(propylene fumarates), poly(ester amides), poly(ethylene fumarates), poly(amino acids), polysaccharides, polypeptides, poly(hydroxy butyrates), poly(hydroxy valerates), polyurethanes, poly(malic acid), polylactides, polyglycolides, polycaprolactones, poly(glycolide-co-trimethylene carbonates), polydioxanones, or copolymers, terpolymers thereof or blends of those polymers, or a combination of biocompatible and biodegradable materials.

In an alternative embodiment of the invention the synthetic biocompatible, biodegradable granules may be porous or hollow instead of being solid granules. The use of hollow

and/or porous granules reduces the amount of implanted material and allows a better in situ integration. In a further advantageous embodiment, the granules may comprise at least one opening in the wall enclosing the interior hollow space, which opening in the wall is larger than micropores in the wall, and being preferably of macroscopic size. By providing the hollow biocompatible and biodegradable granules with an opening in the granule wall, the possibility of a tissue in-growth into the scaffold of the biocompatible and biodegradable implant is enhanced. The hole with an opening in the granule wall may be produced from slurry consisting of the biocompatible material, water and an adhesive (Wintermantel et al. 1996). Droplets of the slurry are brought onto a heated plate. The water in the slurry droplet boils and evaporates instantaneously out of the droplets leaving an evaporation crater in the droplet wall. When the droplets are cooled off, hollow granules having an opening in the granule wall are formed.

Preferably, synthetic biocompatible, biodegradable granules are selected, which have an equivalent-diameter of about 100 μm to about 2000 μm, preferably 500 μm to 1000 μm. Granules of the selected equivalent diameters are easily handled and readily further processed. While the term equivalent-diameter indicates that the synthetic biocompatible and biodegradable granules may be of irregular shape, it is of advantage when it is provided with a regular shape. Preferably it has a generally spherical shape. Due to its homogeneous structure the spherical shape of the granular material allows a better handling and an easier estimation of the required quantity of granular material in order to fill a known volume of a cavity.

A major portion of the granules are coated with at least one biocompatible and biodegradable layer of a polymer preferably selected from the group consisting of poly(α-hydroxyesters), poly(ortho esters), poly(ether esters), polyanhydrides, poly(phosphazenes), poly(propylene fumarates), poly(ester amides), poly(ethylene fumarates), poly(amino acids), polysaccharides, polypeptides, poly(hydroxy butyrates), poly(hydroxy valerates), polyurethanes, poly(malic acid), polylactides, polyglycolides, polycaprolactones, poly(glycolide-co-trimethylene carbonates), polydioxanones, or copolymers, terpolymers thereof or blends of those polymers.

The biocompatible and biodegradable coating layer of the synthetic granules has a thickness of 1 µm to 300 µm, preferably about 5 µm to about 30 µm. The mechanical stability of an implant made of coated granules depends on the thickness and the homogeneity of the coating. By an insufficient coating thickness the granules cannot stick together in the required extent. On the other hand, large amounts of coating materials can lead to the decrease of the pH-value in the vicinity of the implant during its degradation. Therefore, the optimal thickness of the biocompatible coating is a result of a compromise between implant stability and the amount of material, which will degrade. The preferred coating thickness of the granules may also be expressed as a weight fraction of about 4% to about 20% coating materials of the total weight of the scaffold, which may loaded with additives such as plasticizers or biologically active substances. The biocompatible coating is made of a biodegradable polymer. Thus, it is ensured, that after a specified and defined time period the coated granular material may degrade or be resorbed or dissolve within the cavity without any residues.

The synthetic biocompatible, biodegradable granules may be spray-coated, preferably in a fluid bed machine, or immersion-coated with the desired biocompatible polymer(s). Both methods lead to the biocompatible and biodegradable granules having the required properties. The spray coating process in a fluid bed machine is preferred though, because it allows the fabrication of a great number of practically identical polymer-coated biocompatible and biodegradable granules in a very fast and economic manner. The technique is well proven and allows an easy control of the thickness of the coating layer(s) and the fabrication of biocompatible and biodegradable granules having multiple coating layers, which are distinct from each other. The coating in fluidized bed machine results in a homogenous and continuous coating, which offers a barrier against bacterial contamination of the granules or of implants made therefrom. During the coating process the granules do not adhere to each other, thus avoiding the formation of undesirable aggregates which might lead to highly inhomogeneous size distributions and coating thickness. The coated granules retain their excellent free-flow properties, which is necessary for an eventual further processing. Due to the homogeneity of the coating only a low amount of coating material, in particular PLGA, is required for the further consolidation of an implant. Thus, the risks of inflammation or tissue necrosis due to a massive release of acidic products in the environment of an implant during its degradation are significantly reduced. An inte-

gration of additives such as plasticizers or biologically active substances into the coating film(s) may be well controlled by the coating in a fluid bed machine. Thus, each granules is loaded with the same amount of the biologically active substances. The thickness of the coating is well controlled in the process. Therefore, even the release of an integrated biologically active substance is predictable and well controlled.

The coating of the synthetic biocompatible, biodegradable granules may comprise one or more layers of varying average thickness. At least the outmost coating layer is made of a biodegradable material. This embodiment of the invention allows providing the biocompatible and biodegradable granules with several coatings for specific purposes. The outmost biodegradable coating may be selected in accordance with a certain desired delay in degradability. Thus, the coating layer underneath is only exposed after a certain desired time period has expired. This, for example, allows a retarded delivery of a bioactive substance. Thus, the synthetic biocompatible and biodegradable granules may be coated with different coatings, which each is biodegradable and displays a specific effect.

It may be advantageous to provide a biocompatible, biodegradable scaffold, which comprises in addition non-coated synthetic biocompatible granules. The coated and uncoated synthetic granules are thoroughly mixed such, that they are safely fused together by the preferred method of production and still have the required stability. By providing a mixture of coated and non-coated granules for the production of the biocompatible and biodegradable implants, the amount of coating materials, which must degrade, may be further reduced.

The scaffold of the biocompatible, biodegradable implant may consist of one type of synthetic biocompatible, biodegradable granules only. In a preferred embodiment of the invention, the biocompatible, biodegradable implant is made of two or more kinds of coated granules. The term different includes synthetic granules having different sizes. The coated granules are distinct from each other and may consist of different biocompatible materials and/or comprise polymer-coatings, which are distinct from each other. Thus, an implant may be "designed" not only as an ideal match for a bone cavity or an extraction wound

but also in accordance with further specific requirements, such as, for example, stability, resorption kinetic and/or solubility of the implant.

The scaffold of the biocompatible, biodegradable implant may be made of coated granules having micropores with average diameters of about larger than 0 to about 10 µm. By the fusion of the coated granules, the microporosity remains and/or macropores between the granules are formed having average diameters of about more than 10 µm to about 2000 µm, preferably about 100 µm to about 500 µm.

It is to be noted that only the uncoated synthetic biocompatible, biodegradable granules have the claimed porosity. Once the granules are coated the porosity is practically not recognizable any more from the outside. Granules made of bioceramics, which have been sintered very densely, do not have a considerable microporosity at all. The porosity of the granular material and/or the scaffold of the biodegradable implant provides an even larger surface area. In addition the pores may be filled, e.g., with an antibiotic substance, with growth factors and like biologically active substances. Thus, the biocompatible and biodegradable implant, when implanted into a cavity or extraction wound not only fills the cavity, but permits the controlled release of biologically active substances. For example, the substance within the pores may be selected such that bacterial growth and the like more are hindered, such as bone formation is accelerated or such that pain at the bone wound is reduced.

By special selection of the biocompatible and biodegradable materials for the synthetic granules and their coatings, the growth and the proliferation of osteoblast-like cells may be supported during the degradation of the implant, which is finally replaced by newly formed bone tissue. The implant may in certain cases also prevent the erosion of the bone tissue surrounding the bone defect to be healed.

The biodegradable membrane is preferably a polymer film, a polymer textile, a polymer fleece or a layer of interconnected fused polymer particles or a combination thereof and sealed to the scaffold, thus forming at least one layer of impermeability to soft tissue and

epithelial cells. The thickness of the membrane is preferably about 10 µm to about 3000 µm, preferably about 50 µm to about 1000 µm. The thickness can be selected in accordance with the kind of biodegradable polymer, in order to ascertain, that the duration of the degradation and resorption of the polymer membrane matches the duration required for the regeneration of the bone tissue.

In an embodiment of the invention, the membrane is made of a synthetic, biocompatible and biodegradable polymer selected preferably from the group consisting of poly(α-hydroxyesters), poly(ortho esters), poly(ether esters), polyanhydrides, poly(phosphazenes), poly(propylene fumarates), poly(ester amides), poly(ethylene fumarates), poly(amino acids), polysaccharides, polypeptides, poly(hydroxy butyrates), poly(hydroxy valerates), polyurethanes, poly(malic acid), polylactides, polyglycolides, polycaprolactones, poly(glycolide-co-trimethylene carbonates), polydioxanones, or co-polymers, terpolymers thereof or blends of those polymers

The membrane may be formed by fusing polymer particles together such as for example microspheres, pellets or granules, having a size smaller than about 500µm, preferably having a size about 1 µm to 200 µm.

The fusing of polymer pellets for the creation of the membrane may lead to the formation of pores in the membrane with sizes in the range of 1 µm to 500 µm, preferably of 5 µm to 50 µm. The size of the pores depends on the size of the polymer particles. The size of the particles is so selected such that the membrane may be porous, allowing the transport of fluids, but forming a barrier against soft tissue and/or epithelial cells in growth into the implant. The porosity can enhance the vascularization of the implant and, thus, promote the healing of the implantation site

In a further embodiment of the invention, the membrane has at least two layers, one layer having a barrier function against soft tissue and/or epithelial cells in-growth in the scaffold and the second layer, which is direct in contact with the surrounding living organism

serving for a stabilization and anchorage of the soft tissue which tends to close the wound, e.g. the stabilization of the gingival flap in the case of a tooth extraction wound.

In an alternative embodiment of the biodegradable, biocompatible implant at least one layer of the membrane is non-porous. The non-porous layer of the membrane prohibits the transport of fluids and the migration of microscopic materials, such as, e.g., bacteria, through the membrane. Thus, precautionary antibiotic measures may be omitted.

In a further embodiment of the invention a biologically active substance is integrated into the synthetic granules and/or into the coating, and/or forming a coating layer itself. Thus, a controlled delivery of the biologically active substance is enabled. The amount of the biologically active substance may easily be defined by controlling the coating process, for example. By integrating biologically active substance into a submerged coating layer or into the granular material itself, a controlled retarded release of the biologically active substance may be accomplished. The biological active substance can be also encapsulated in biodegradable microspheres and added to the granules for the preparation of the scaffolds and/or the membrane.

The biocompatible, biodegradable implant may be used for tissue engineering applications. Hence, cells may be grown on the said implant. In another embodiment of the invention, the biocompatible, biodegradable implant may be seeded with cells.

The invention also suggests an easy to accomplish method for the production of an biodegradable, biocompatible implant for the treatment of defects in a living organism such as bone defects or extraction wounds. The method comprises the fusing of synthetic, biocompatible and biodegradable granules through polymer linkage within a mold to form a scaffold. A biodegradable polymer film, a biodegradable fleece, a biodegradable textile, biodegradable polymer granules, or a combination thereof is added on top of the scaffold within a mold and, through polymer linkage, is sealed to the scaffold. A membrane is hence created on a part of the implant creating a at least one zone of impermeability against soft tissue and/or epithelial cells in-growth.

The linkage of the synthetic granules is accomplished by subjecting them for a time span of at least about 3 seconds, typically for about 15 seconds to about 180 seconds to a pressurized CO_2 atmosphere, at a pressure of about 20 bar to about 200 bar, preferably about 50 bar and at a temperature of about 10°C to about 100°C, preferably about 20°C to about 37°C. The linkage of the biodegradable polymer film, the biodegradable fleece, the biodegradable textile, the biodegradable fused polymer particles, or a combination thereof may be performed simultaneously with the linkage process of the scaffold, or it may be performed in a second, separate step. If a second linkage step is required, the biodegradable polymer film, the biodegradable fleece, the biodegradable textile, the biodegradable fused polymer particles, or a combination thereof are linked with each other and with the surface of the scaffold within the mold by subjecting the contents of the mold for a further time span of at least about 3 seconds, typically for about 15 seconds to about 180 seconds, to a pressurized CO_2 atmosphere at a pressure of about 20 bar to about 200 bar, and at a temperature of about 10°C to about 100°C, more preferably about 20°C to about 37°C.

The CO_2 atmosphere acts as a slight solvent with respect to the polymer-coated granules and to the polymer film or the polymer granules of the barrier membrane. It enhances the linkage of the granules of the scaffold and of the barrier membrane with each other ensures a linkage of the polymer barrier membrane with the surface of the scaffold. The produced biocompatible and biodegradable scaffolds preferably comprise macropores in between the fused together synthetic granules. The macropores may be interconnected and have average sizes from about 10 µm to about 2000 µm, preferably about 100 µm to about 500 µm. The macropores serve to enhance the in-growth of tissue into the scaffold and thus allow a faster regeneration of the healing site.

In an alternative production method the synthetic granules are fused to a scaffold together with the membrane in the form of a biodegradable polymer film, a biodegradable fleece, a biodegradable textile, biodegradable fused polymer particles, or a combination thereof within a mold by subjecting the materials for a time span of at least about 10 seconds, typically of about 30 seconds to about 5 minutes to a heat treatment at elevated temperatures of about 50°C to about 220°C, preferably about 80°C to about 85°C.

When additives such as plasticizers, are integrated into the polymer coating of the granules of the scaffold and/or in the material of the membrane, the glass transition temperature of polymeric material can be reduced. Hence, the process temperature for the fusion of scaffold and the membrane can be reduced as far as to room temperature or even lower.

The porosity of the membrane may be reduced by subjecting the membrane to a final heat treatment, preferably by exposure to an infra-red lamp or the like, at a temperature of about 100°C to about 220°C, preferably 120°C to 140°C for a time span of about 1 s to about 120 s, preferably about 20 s to 60 s. This additional heat treatment process allows to prepare a barrier membrane without any porosity.

A preferred field of use for the biocompatible, biodegradable implant according to the invention is the application as a temporary replacement for an extracted tooth root or the like. Fusing of the individual synthetic polymer-coated granules to a matching scaffold and the addition of a barrier membrane may be accomplished very easily and very fast on-site from prefabricated biocompatible and biodegradable particles.

The biocompatible, biodegradable implants are made from coated granules of a synthetic, biocompatible and biodegradable material. They may also comprise uncoated granules. The granules are preferably fused together in a mold having a cavity corresponding to the required shape. The barrier membrane is formed and linked with the scaffold of the biodegradable biocompatible implant within the mold by a CO_2 process or by a heat treatment. After removal from the mold, the biodegradable biocompatible implant needs not be finished but may be directly inserted into a bone cavity or an extraction wound. However, due to the relatively high stability of the implants, they may even be further finished, such as, for example, by cutting away portions of the implant, if the need arises.

The incorporation of biologically active substances, such as growth factors for example, into a biocompatible, biodegradable implant may also be achieved very easily by mixing loaded microspheres with the synthetic biocompatible,biodegradable coated granules

and/or particles. This allows a manufacture of the coated granules and/or particles under non-aseptic conditions with subsequent sterilization, while the microspheres, which carry the growth factors, may be produced under aseptic conditions. The mixing of the coated granules and the microspheres is done just before the preparation the biocompatible and biodegradable implant. The bonding is preferably achieved in a gaseous CO_2 atmosphere at low temperatures of about 20°C to about 37 °C, and a pressure of about 20 bar to about 200 bar, preferably about 30 bar to about 40 bar. Under these conditions and at such low temperatures, the growth factors may be handled easily with only little danger of degradation or alteration.

The preparation of the implant may be also be accomplished by a thermal process. However, the process parameters, such as, e.g., the temperature, must be carefully selected in order to prevent any degradation or alteration of the biological active substances.

BRIEF DESCRIPTION OF THE DRAWINGS

Further advantages of the invention will become apparent from the description of exemplary embodiments of the invention with reference to the accompanying drawings in which:

Fig. 1 is a schematic representation of a biodegradable biocompatible implant according to the invention;

Figs. 2a and 2b are electron microscope cross sectional views of a biodegradable biocompatible implant with a non-porous membrane;

Fig. 3 is an electron microscope cross sectional view of a non porous membrane formed from fused polymer particles;

Fig. 4a is an electron microscope cross sectional view of a biodegradable biocompatible implant with a macro-porous membrane;

Fig. 4b is an electron microscope top plan view of the macro porous membrane;

Figs. 5a and 5b are electron microscope cross sectional views of a biodegradable biocompatible implant with a micro-porous membrane; and

Fig. 6 is a schematic representation of a preformed biodegradable biocompatible implant according to the invention, where the membrane exceeds the scaffold in size.

DETAILED DESCRIPTION OF THE INVENTION

Fig. 1 is a schematic drawing of a biodegradable biocompatible implant according to the invention. More specifically, the representation shows a biocompatible and biodegradable implant 1 for implantation into a tooth extraction wound which is left by an extracted tooth in the alveolar bone. The biodegradable biocompatible implant 1 is shaped according to the root of the extracted tooth. It is produced from granules 2 of a synthetic, biocompatible and biodegradable material, such as, e.g., tricalcium phosphate (TCP). The granules 2 generally are of a regular, preferable spherical, shape. They may be solid or hollow with an opening in the granule wall. At least a portion of the granules 2 is provided with a coating of a biocompatible and biodegradable polymer. The coating is e.g. a polylactide and encloses the granules 2 completely like a shell. It has a thickness of about 1 µm to about 300 µm, preferably about 5 µm to about 20 µm. Coated and uncoated granules are fused together to form a scaffold 3 of interconnected granules. The interconnection is accomplished by polymer linkage of the polymer coating of neighbouring coated granules 2.

The upon implantation exposed upper surface of the scaffold 3 is covered with a barrier membrane 4 which is made of a biocompatible and biodegradable polymer, such as, e.g.

polylactide. The barrier membrane 4 is interconnectibly sealed to the surface of the scaffold 3 such, that scaffold 3 and membrane 4 form a single piece of matter.

In Fig. 6, the representation shows a preformed biodegradable biocompatible implant 1 according to the invention, which is similar as the implant as described in Fig. 1. However, more than one exposed surface of the open porous scaffold 3, made of coated granules 2 is covered by a membrane 4. The membrane 4 exceeds the scaffold in size to prevent soft tissue and/or epithelial cells in-growth at the interface between bone and the biodegradable biocompatible implant.

Synthetic base material for granules:

Preferred biodegradable materials include bioceramics such as calcium phosphates and calcium sulfates, bioglasses, and mixtures thereof. The calcium-based ceramics include, as monocalcium phosphate monohydrate (MCPM, $Ca(H_2PO_4)_2.H_2O$), monocalcium phosphate anhydrous (MCPA, $Ca(H_2PO_4)_2$), tetracalcium phosphate (TetCP, $Ca_4(PO_4)_2O$), calcium orthophosphate phosphate (OCP, $Ca_8H_2(PO_4)_6.5H_2O$), calcium pyrophosphate (CaP, $Ca_2P_2O_7$), dicalcium phosphate anhydrous (DCP, $CaHPO_4$), dicalcium phosphate dihydrate (DCPD, $CaHPO_4.2H_2O$), β-tricalcium phosphate (β-TCP, $Ca_3(PO_4)_2$), α-tricalcium phosphate (α-TCP, $Ca_3(PO_4)_2$), and apatite such as hydroxyapatite (HA, $Ca_{10}(PO_4)_6(OH)_2$). Calcium phosphate ceramics are known for their excellent biocompatibility and are therefore used in various biomedical applications, HA and TCP among them being the most used bioceramics in orthopedic and maxillo-facial applications and for the treatment of bone defects. Their close ionic similarity with the mineral components of bone, their adjustable resorption kinetics to the need of a specific therapy and their bioactive properties have been mentioned before in the prior art. While HA is commonly considered to be non-biodegradable, some resorption behavior has been reported in in-vivo studies (Oonishi et al. 1999). β-TCP is generally considered to be biodegradable and is known to degrade faster than HA. After resorption of TCP in vivo new bone tissue is reported to replace the resorbed materials.

Preparation of β-TCP granules:

From β-TCP powder granules are prepared, for example, by a spheronization route. 70g β-TCP powder (purum p.a. >96%, Fluka, CH) is mixed with 1g dextrin (Relatin Dextrin K51) in a mortar. 20 ml deionized water is slowly added to the powdery mixture under continuous stirring. The resultant paste is extruded through a multi-hole (ø: 800µm) nozzle (Cyclo, Typ XYCG, Probst Technik, CH) and spheronized during ca. 3 min in a pelletrounder (Probst Technik, CH) in order to obtain granules having an average diameter of about 350 µm to about 1000 µm. The obtained β-TCP granules with a diameter between 500 and 1000µm are then calcinated and sintered at a temperature of 1150°C during 4 hours in a furnace (Nabertherm, CH).

Other method such as high-shear mixer and fluidized bed granulation can also be used in order to produce rounded granules.

Biocompatible and biodegradable polymer-coating of granules:

Meanwhile a large number of biocompatible and biodegradable polymers are known from the prior art, among poly(α-hydroxyesters), poly(ortho esters), poly(ether esters), polyanhydrides, poly(phosphazenes), poly(propylene fumarates), poly(ester amides), poly(ethylene fumarates), poly(amino acids), polysaccharides, polypeptides, polyurethanes, poly(malic acid), polylactides, polyglycolides, polycaprolactones, poly(glycolide-co-trimethylene carbonates), polydioxanones, or copolymers, terpolymers thereof or blends of those polymers. By way of example only the invention will be illustrated with reference to poly-lactide-co-glycolide (PLGA), which is known for its biocompatibility and biodegradability. For this purpose, a solution of PLGA in dichloromethan (CH_2Cl_2) is first prepared. The concentration of the polymer was about 0.1g to 0.2g PLGA in 1ml CH_2Cl_2. The β-TCP granules are immersed in the PLGA solution. While the resultant mixture is constantly stirred, the solvent evaporates until a thin film of polymer is deposed on the surface of the β-TCP granules. Agglomerated granules can be then separated using a labor mixer and sieved. The extraction of the solvent is finally carried out for 36h under vacuum (100mbar).

A far more economic coating method, which results in a very homogenous coating of the β-TCP granules is the spray coating process in a fluidized bed machine. This coating process is well known from the prior art and has proven to achieve the desired homogenous coating results.

It is apparent to those skilled in the art that by selecting different coating solutions and varying the coating time, different layers of coatings having different thicknesses may be applied to the β-TCP granules. This includes the coating with biologically active substances as an individual coating or mixed or dissolved in the polymer coating.

Preparation of scaffolds for biocompatible and biodegradable implants:

β-TCP-PLGA biodegradable biocompatible implants are prepared from β-TCP granules, which are coated with at least one layer of PLGA. Various methods for the fabrication of implants may be used in order to fuse the polymer-coated granules together, among them heat treatments, application of solvents, use of pressurized CO_2, chemical linkage, mechanical fusion by applying pressure, and mixtures of those methods.

Process A

By a fusion method, which applies a heat treatment at elevate temperatures the scaffold of the biocompatible and biodegradable implant may be prepared as follows:

700mg PLGA coated β-TCP granules are poured into a polysiloxane mold, having the desired shape, and heated to a temperature of about 80°C to about 100°C. The granules are slightly compressed in the mold and kept at 80°C to about 100°C for at least about 5 seconds. Typically the process time amounts to about 10 seconds to about 5 minutes, preferably for about 1 minute to about 3 minutes.

Process B

The fusing of coated granules applying a method using pressurized CO_2 may be carried out as follows:

After filling a polysiloxane mold with a desired shape with 700mg PLGA coated β-TCP granules, the mold is place in a high pressure vessel at room temperature. After closure of the vessel, CO_2 is introduced into the vessel until a pressure of about 50 bar is reached. The pressure is increased at a ramp of about 2 bar per second. Once the maximum pressure is reached, it is held for at least about 3 seconds. Typically the pressure is held for about 3 seconds to about 180 seconds, preferably less than 30 seconds. Then, the CO_2 pressure is decreased at a rate of about 0.5 bar per second until it equilibrates with the outer atmospheric pressure. The whole process is preferably performed at room temperature or at slightly elevated temperatures of about 24°C to about 37°C. Such an implant has a porosity of ca. 55% and a median pore diameter of ca. 280 µm.

Since the β-TCP granules are homogeneously coated with PLGA they are capable of fusing together during the CO_2 treatment. The CO_2 acts as a solvent for the coating. This results in a decrease of the glass transition temperature (T_g) of the polymer below the processing temperature. By the combination of the gas pressure and the reduction of T_g the granules are able to fuse by polymer linkage only. Thus, it is apparent that a homogenous coating of the granular base material is an essential prerequisite for the fusing of the coated granules. The implants comprise interstitial spaces in between the fused granules. The size of the interstitial spaces is depending on the thickness of the coating, on the compaction of the implant, and on the size of the coated granules. Thus, an application of moderate additional pressure on the mold cavity during the fusing of the granules reduces the interstitial space and allows a control thereof. A scaffold having larger interstitial spaces may be desirable in order to provide room for the in-growth of newly formed tissue.

Preparation of scaffolds of biocompatible and biodegradable implants loaded with biologically active substances:

Process B using pressurized CO_2 for the fusing of the synthetic granules is preferred, because it permits to produce biocompatible and biodegradable scaffolds including, for example, PLGA microspheres loaded with biologically active substances such as insulin like growth factor-1 (IGF-1).

The preparation of biocompatible and biodegradable implants loaded with IGF-1 may be carried out as follows:

25 mg PLGA microspheres loaded with IGF-1 were mixed in a polysiloxane mould with 950 mg of coated granules using a small spatula. The granules used for this experiment were coated with PLGA in order to achieve a material compatible interface between the granules and the microspheres. For a homogenous microsphere distribution through the scaffold, the polysiloxane mould filled with the biomaterials was vibrated with a vortex device (level 3, Vortex Genie 2, Bender & Hobein, CH) during 20s. In order to prevent the segregation of the microspheres on the bottom of the mould, the mould was turned upside down and the vibrating was repeated. The consolidation of the scaffold was then achieved under pressurized CO_2 atmosphere at 30 bar during 60 s.

Preparation of the barrier membrane and sealing to the exposed surface of the scaffold:

The barrier membrane may be made of a polymer film, a polymer fleece, a polymer textile, a layer of fused polymer particles or a combination thereof.

Example 1:

For the preparation of a polymer film, PLGA may be used. The polymer powder is first compressed between two plates with a load of 100 kN at 140 °C during 10 min. With this process a polymer film having a thickness of about 200 µm is obtained. The film is cut into small pieces of about 10 mm x 10 mm.

A scaffold is prepared in accordance with process A. Briefly, a mold is filled with β-TCP granules which are coated with PLGA. During the heat treatment the granules are gently

compressed within the mold. After about 1 min to 3 min a piece of the polymer film is placed on the exposed surface of the scaffold. Because of the elevated temperature of the scaffold the film is malleable and may be easily manipulated in order to cover the entire surface of the scaffold. The polymer film links with the polymer coating of the coated granules of the scaffold. After cooling of the mold, the implant may be removed out of the mold. The implant is provided with a barrier membrane having a non-porous surface. This is shown in the cross sectional views in Figs. 2a and 2b in which the large granules belong to the scaffold and the smooth film represents the non-porous barrier membrane. Even in the larger magnification in Fig. 2b no pores are visible on the surface of the membrane.

Example 2:

Polymer ganules are prepared from PLGA powder. The powder is compressed between two plates with a pressure of 100 kg/m² at 130°C for about 40 min. After cooling a solid plate having a thickness of about 500 µm is obtained. The solid plate is cut into pieces which are ground in a centrifugal mill. After milling polymer granules with a size of about 100 µm to about 200 µm are obtained.

A scaffold is prepared in accordance with the process in Example 1. The mold is then placed under an infra-red lamp which allows to heat the surface part of the polymer barrier membrane at about 130°C. After about 30 s of heat treatment the mold and the implant are allowed to cool. The implant is removed out from the mold. The implant is provided with a non-porous barrier membrane as is depicted in the electron microscope cross sectional view in Fig. 3.

Example 3:

The scaffold and the polymer particles are prepared as in Example 2. About 50 mg to 100 mg of polymer particles are poured into the mold on the exposed surface of the scaffold. After about 1 min to about 3 min at 80°C to 100°C the polymer granules have linked with each other and with the surface of the scaffold. The mold is allowed to cool and the bio-

degradable biocompatible implant is removed. With this process a biodegradable biocompatible implant is achieved having a barrier membrane sealed to its surface which is macro-porous. The pores have sizes within a range of about 100 µm to about 500 µm. This is clearly shown in the cross sectional view in Fig. 4a, in which the large granules form a part of the scaffold while the smaller particles are a part of the barrier membrane. The top plan view of Fig. 4b shows the porosity of the exposed surface of the barrier membrane.

Example 4:

Polymer microspheres are prepared from PLGA. The microspheres are prepared using an emulsion/solvent extraction method. For that purpose first a polymer solution in ethyl acetate (6.25% w/w) is prepared. The solution is introduced dropwise into stirred PVA solution (0.4% w/w) such that an emulsion is formed. The emulsion is poured into 800 ml of water and stirred during about 5 h. The resulting solution is filtered. The obtained microspheres are dried under vacuum for about 12 h. The resulting microspheres have a size in the range from about 40 µm to about 100 µm.

The scaffold is prepared by heat treatment as before in Examples 1 - 3. About 50 mg to 100 mg of the polymer microspheres are poured into the mold on the exposed surface of the scaffold. After about 1 min to about 3 min at 80°C to 100°C the polymer microspheres have linked with each other and with the surface of the scaffold. The mold is allowed to cool and the implant is removed out of the mold. With this process a biodegradable biocompatible implant is achieved having a barrier membrane sealed to its surface which is micro-porous. The pores have sizes within a range of about 5 µm to about 30 µm. This is shown in the cross sectional views in Figs. 5a and 5b. In Fig. 5a large granules form a part of the scaffold while the smaller microspheres are a part of the micro-porous barrier membrane.

The biodegradable biocompatible implant according to the invention is a combination of a biocompatible and biodegradable scaffold which is shaped in accordance with the shape of the bone defect, and of a biocompatible and biodegradable barrier membrane which prohibits the in-growth of soft tissue and epithelial cells. The barrier membrane is inter-

connectively sealed to the exposed surface of the scaffold such that the biodegradable biocompatible implant forms a single piece of matter. The barrier membrane on the finished biodegradable biocompatible implant matches the form of the exposed surface of the scaffold. There is no need for an alignment of the membrane on the scaffold. There is no more surgery necessary to fix the barrier membrane or, subsequently, to remove the membrane. Both, the scaffold of the biodegradable biocompatible implant and the barrier membrane are biodegradable. Thus, they need not be removed from the healing site, but they are completely resorbed by the organism. The biodegradable biocompatible implant according to the invention is easy and cheap to manufacture. The preparation may be accomplished on site, e.g., by a physician or an assistant. While the invention has been described with reference to biodegradable biocompatible implants for dental applications it will be appreciated by those skilled in the art that the biodegradable biocompatible implants may also be used for the repair of bone defects of other skeleton parts. If, for example, a part of the skeleton is stricken by a tumor, the area stricken by the tumor may be removed and replaced by a biodegradable biocompatible implant according to the invention.

CLAIMS:

1. Biodegradable, biocompatible implant for the treatment of defects in a living organism such as bone defects or tooth extraction wounds, comprising at least one zone of impermeability to soft tissue and/or epithelial cells in-growth, wherein said implant is made of an open porous scaffold and a membrane covering at least a part of said scaffold and being sealed to it such that said scaffold and said membrane form a single piece of matter.

2. Biodegradable, biocompatible implant according to claim 1, wherein said scaffold is made of a synthetic, biocompatible and biodegradable material, such as biopolymers, bioglasses, bioceramics, more preferably calcium sulfate, calcium phosphate such as, for example, monocalcium phosphate monohydrate, monocalcium phosphate anhydrous, dicalcium phosphate dihydrate, dicalcium phosphate anhydrous, tetracalcium phosphate, calcium orthophosphate phosphate, calcium pyrophosphate, α-tricalcium phosphate, β-tricalcium phosphate, apatite such as hydroxyapatite, or polymers such as, for example, poly(α-hydroxyesters), poly(ortho esters), poly(ether esters), polyanhydrides, poly(phosphazenes), poly(propylene fumarates), poly(ester amides), poly(ethylene fumarates), poly(amino acids), polysaccharides, polypeptides, poly(hydroxy butyrates), poly(hydroxy valerates), polyurethanes, poly(malic acid), polylactides, polyglycolides, polycaprolactones, poly(glycolide-co-trimethylene carbonates), polydioxanones, or copolymers, terpolymers thereof or blends of those polymers, or a combination of biocompatible and biodegradable materials.

3. Biodegradable, biocompatible implant according to claims 1 or 2, wherein said scaffold is made of fused, biocompatible, biodegradable granules selected from the group consisting of solid granules, porous granules, hollow granules, hollow granules with at least one opening in the granule hole, or a mixture thereof; said granules having an equivalent-diameter of about 100 μm to about 2000 μm, preferably 500 μm to 1000 μm; and are preferably of a regular shape, such as, for example, a spherical shape; a major portion of said granules being coated with at least one biocompatible and biodegradable layer of a polymer selected from the group consisting of poly(α-hydroxyesters), poly(ortho esters), poly(ether esters), polyanhydrides, poly(phosphazenes), poly(propylene fumarates), poly(ester amides), poly(ethylene fumarates), poly(amino acids), polysaccharides, polypeptides, poly(hydroxy butyrates), poly(hydroxy valerates), polyurethanes, poly(malic acid), polylactides, polyglycolides, polycaprolactones, poly(glycolide-co-trimethylene carbonates), polydioxanones, or copolymers, terpolymers thereof or blends of those polymers; and said polymer coating having a thickness of 1 μm to 300 μm, preferably about 5 μm to about 30 μm.

4. Biodegradable, biocompatible implant according to any one of the preceding claims, wherein said scaffold has an open porous configuration with interconnected pores having a size of about 10 μm to about 2000 μm, preferably about 100 μm to about 500 μm.

5. Biodegradable, biocompatible implant according to any one of the preceding claims, wherein said membrane is made of synthetic, biocompatible and biodegradable polymer selected from the group consisting of poly(α-hydroxyesters), poly(ortho esters), poly(ether esters), polyanhydrides, poly(phosphazenes), poly(propylene fumarates), poly(ester amides), poly(ethylene fumarates), poly(amino acids), polysaccharides, polypeptides, poly(hydroxy butyrates), poly(hydroxy valerates), polyurethanes, poly(malic acid), polylactides, polyglycolides, polycaprolactones, poly(glycolide-co-trimethylene carbonates), polydioxanones, or copolymers, terpolymers thereof or blends of those polymers.

6. Biodegradable, biocompatible implant according to one of the preceding claims, wherein said biodegradable membrane is a polymer film, a polymer textile, a polymer fleece, a layer of fused polymer particles or a combination thereof, thus forming at least one zone of impermeability to soft tissue and/ or epithelial cells in-growth, and having a thickness of about 10 μm to about 3000 μm, preferably about 50 μm to about 1000 μm.

7. Biodegradable, biocompatible implant according to any one of the preceding claim, wherein said biodegradable membrane is made of fused polymer particles, such as, for example, microspheres, pellets or granules, having a size smaller than about 500 μm, preferably having a size about 1 μm to 200 μm.

8. Biodegradable, biocompatible implant according to any one of the preceding claims, wherein said membrane has a configuration such as to allow a transport of fluids and/or molecules through the membrane, but forming a barrier against soft tissue and/or epithelial cells in-growth into the implant.

9. Biodegradable, biocompatible implant according to any of the preceding claims, wherein at least a portion of the said membrane has a porous configuration, said porosity being formed by pores having sizes in the range of about 1 μm to 500 μm, preferably 5 μm to 50 μm.

10. Biodegradable, biocompatible implant according to any one of the preceding claims, wherein said membrane comprises at least two layers, one of said layers having a barrier function against soft tissue and/or epithelial cells in-growth in the scaffold, and a second layer, which is direct in contact with the surrounding living organism, allowing the stabilization and anchorage of soft tissue which tends to close the wound.

11. Biodegradable, biocompatible implant according to any one of the preceding claims, wherein said membrane comprises at least one non-porous layer.

12. Biodegradable, biocompatible implant according to any one of the preceding claims, further comprising at least one biologically active substance which is integrated in said scaffold and/or into said membrane and/or which is encapsulated in microspheres which are loaded into said scaffold and/or into said membrane.

13. Biodegradable, biocompatible implant according to any one of the preceding claims, further comprising at least one additive such as a plasticizer, which is integrated into said scaffold and/or into said membrane.

14. Biodegradable, biocompatible implant according to any one of the preceding claims, wherein an exposed surface of said biodegradable biocompatible implant allows cell growth into the scaffold.

15. Biodegradable, biocompatible implant according to any one of the preceding claims, wherein said biodegradable and biocompatible implant is seeded with cells.

16. Method for the preparation of a biodegradable, biocompatible implant for the treatment of defects in a living organism such as bone defects or tooth extraction wounds, characterized by fusing together an open porous scaffold and at least one membrane, which is preferably made of a polymer film, a polymer fleece, a layer of fused polymer particles or a combination thereof, within a mold, thus, creating at the surface of the said implant at least one zone of impermeability against soft tissue and/or epithelial cells in-growth.

17. Method according to claim 16, wherein the said open porous scaffold and the said membrane are fused together by subjecting them for a time span of at least about 3 seconds, typically for about 15 seconds to about 180 seconds to a pressurized CO_2 atmosphere, said CO_2 atmosphere having a pressure of about 20 bar to about 200 bar, preferably about 50 bar, at a temperature of about 10°C to about 100°C, preferably about 20°C to about 37°C.

18. Method according to claim 16, wherein the said open porous scaffold and the said membrane are fused together by subjecting them for a time span of at least about 10 seconds, typically of about 30 seconds to about 5 minutes to a heat treatment at elevated temperatures of about 50°C to about 220°C, preferably about 80°C to about 85°C.

19. Method according to any one of claims 16 - 18, wherein after fusing together said scaffold and said membrane, said membrane is subjected to a final heat treatment, preferably by exposure to an infra-red lamp or the like, at a temperature of about 100°C to about 220°C, preferably 120°C to 140°C, for a time span of about 5 s to about 120 s, preferably about 20 s to 60 s.

20. Method according to any one of claims 16 - 19, wherein said open porous scaffold is made of synthetic, biocompatible and biodegradable materials, such as biopolymers, bioglasses, bioceramics, more preferably calcium sulfate, calcium phosphate such as, for example, monocalcium phosphate monohydrate, monocalcium phosphate anhydrous, dicalcium phosphate dihydrate, dicalcium phosphate anhydrous, tetracalcium phosphate, calcium orthophosphate phosphate, calcium pyrophosphate, α-tricalcium phosphate, β-tricalcium phosphate, apatite such as hydroxyapatite, or polymers such as, for example, poly(α-hydroxyesters), poly(ortho esters), poly(ether esters), polyanhydrides, poly(phosphazenes), poly(propylene fumarates), poly(ester amides), poly(ethylene fumarates), poly(amino acids), polysaccharides, polypeptides, poly(hydroxy butyrates), poly(hydroxy valerates), polyurethanes, poly(malic acid), polylactides, polyglycolides, polycaprolactones, poly(glycolide-co-trimethylene carbonates), polydioxanones, or copolymers, terpolymers thereof or blends of those polymers, or a combination of biocompatible and biodegradable materials; said open porous scaffold having an open porous configuration with interconnected pores having a size of about 10 μm to about 2000 μm, preferably about 100 μm to about 500 μm; and said membrane being made of a synthetic, biocompatible and biodegradable polymer selected from the group consisting of poly(α-hydroxyesters), poly(ortho esters), poly(ether esters), polyanhydrides, poly(phosphazenes), poly(propylene fumarates), poly(ester amides), poly(ethylene fumarates), poly(amino acids), polysaccharides, polypeptides, poly(hydroxy butyrates), poly(hydroxy valerates), polyurethanes, poly(malic acid), polylactides, polyglycolides, polycaprolactones, poly(glycolide-co-trimethylene carbonates), polydioxanones, or copolymers, terpolymers thereof or blends of those polymers; said membrane being preferably in the form of a polymer film, a polymer textile, a polymer fleece, a layer of fused polymer particles or a combination thereof; and said membrane forming at least one zone of impermeability against soft tissue and/or epithelial cells in-growth into said implant.

21. Method according to any one of claims 16 - 20, wherein the said scaffold is made of fused biocompatible and biodegradable granules which are selected from the group consisting of solid granules, porous granules, hollow granules, hollow granules with at least one opening in the granule hole, or a mixture thereof; said granules having an equivalent-diameter of about 100 μm to about 2000 μm, preferably 500 μm to 1000 μm, and preferably being of a regular shape, such as, for example, a spherical shape; and a major portion of said granules being coated with at least one biocompatible and biodegradable polymer layer having a thickness of about 1 μm to about 300 μm, preferably about 5 μm to about 30 μm.

ABSTRACT

There is described a biodegradable, biocompatible implant for the treatment of defects in a living organism, for example, a bone defect or a tooth extraction wound, comprising an open porous scaffold, and further comprising a membrane which is interconnectibly sealed to a surface portion of the scaffold such, that the scaffold and the membrane form a single piece of matter.

(Fig. 1)

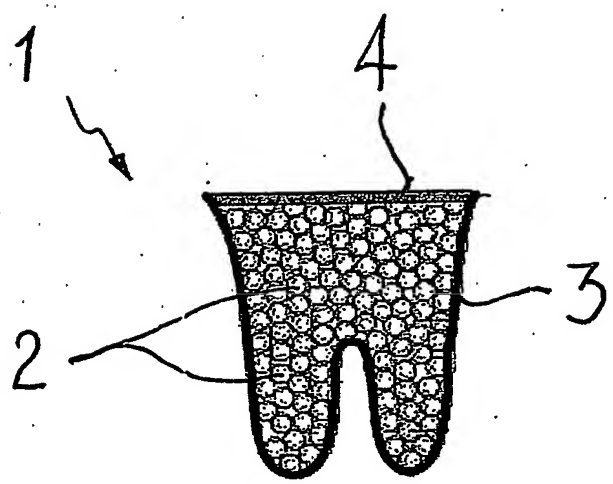

Fig. 1

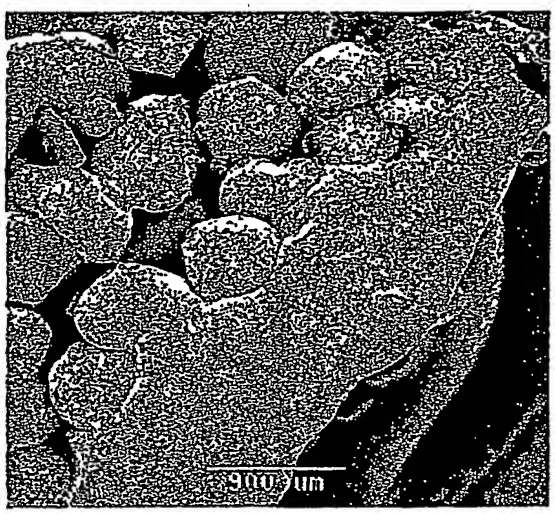

Fig. 3

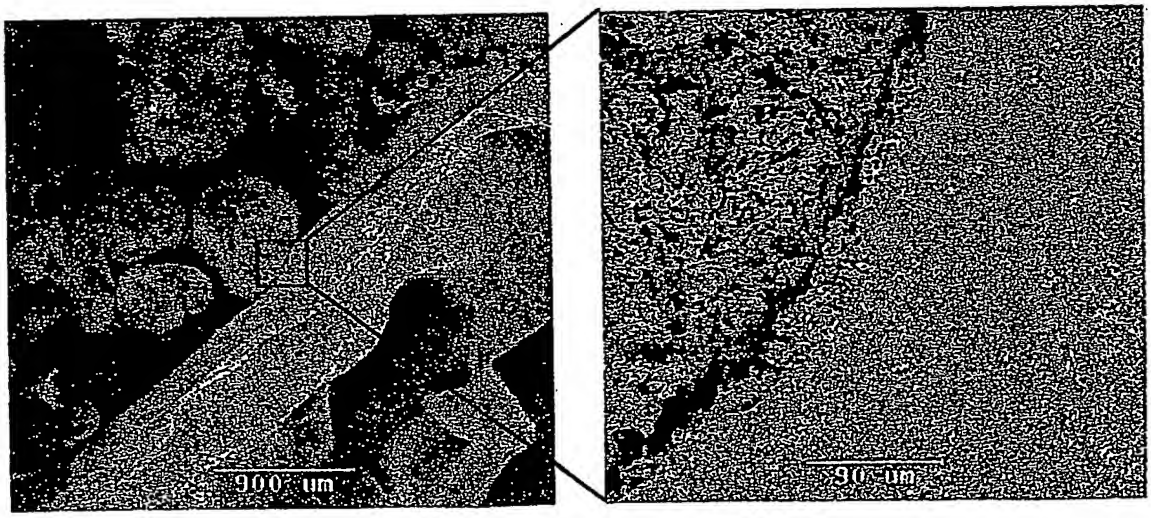

Fig. 2a

Fig. 2b

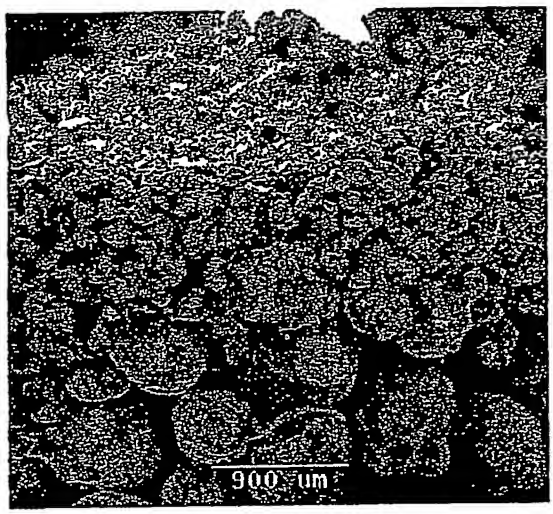

Fig. 4a

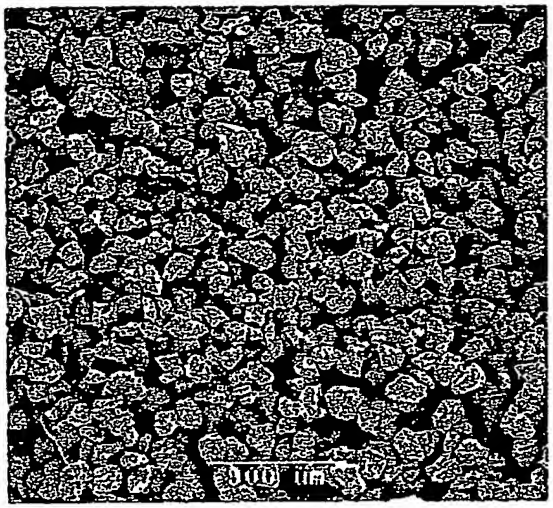

Fig. 4b

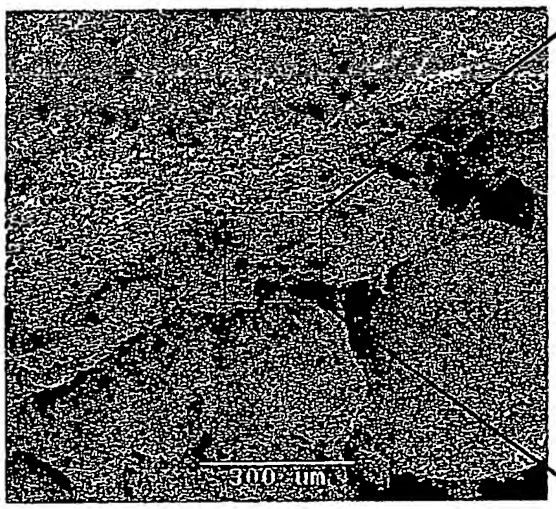

Fig. 5a

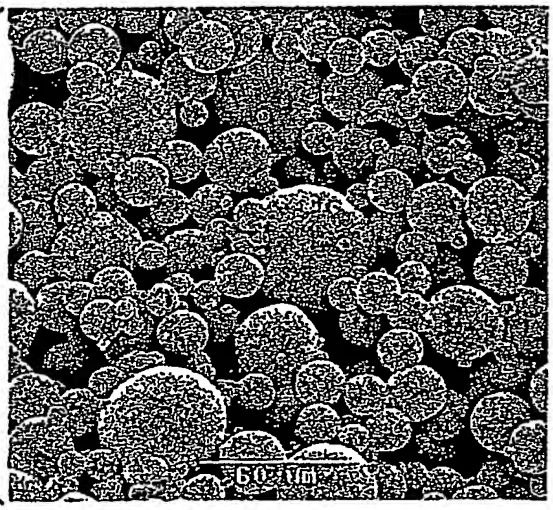

Fig. 5b

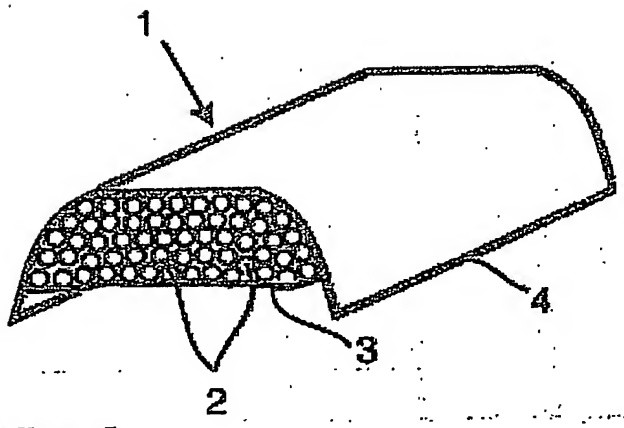

Fig. 6